Comparative Fasting Bioavailability of 2 Bepotastine Formulations in Healthy Male Chinese Volunteers: An Open-Label, Randomized, Single-Dose, 2-Way Crossover Study

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ABSTRACT

Background: Bepotastine is a second-generation histamine$_1$ receptor antagonist that is used in the treatment of allergic rhinitis, urticaria, and pruritus associated with skin disease. A new generic formulation of bepotastine has been developed in China, and information concerning bioavailability and pharmacokinetic properties in the Chinese population has not been reported.

Objective: The aim of the present study was to compare the bioavailability and pharmacokinetic properties of 2 tablet formulations of bepotastine, the 10-mg generic formulation (test) and a branded formulation (reference), in healthy male Chinese volunteers to obtain registration approval of the test formulation.

Methods: A single-center, open-label, randomized, 2-way crossover study with a 1-week washout period was conducted in 24 healthy male volunteers. Blood samples were collected for 16 hours after a single dose of the 10-mg bepotastine test formulation or the reference formulation. Plasma bepotastine concentrations were determined using a validated LC-MS/MS method. C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, and $t_{½}$ were determined using noncompartmental analysis. The formulations were considered bioequivalent if the 90% CIs for the log-transformed C_{max} and AUC values were within the predetermined interval of 75% to 133% and 80% to 125%, respectively, according to the guidelines of the China Food and Drug Administration.

Results: No significant differences were found in mean (SD) pharmacokinetic parameters between the test and reference drugs, including C_{max} (74.81 [9.91] ng/mL vs 78.60 [29.58] ng/mL), AUC_{0-t} (295.55 [115.29] ng · h/mL vs 299.17[109.29] ng · h/mL), and $AUC_{0-\infty}$ (305.28 [118.50] ng · h/mL vs 310.90 [112.20] ng · h/mL). The mean (SD) $t_{½}$ values of the test and reference formulations were 2.53 (0.50) hours and 2.62 (0.41) hours, respectively. The 90% CIs of the treatment ratios for the logarithmic transformed values of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 86.96% to 101.80%, 93.22% to 104.13%, and 92.66% to 103.30%, respectively. All values were within the predetermined bioequivalence range. Two adverse events were reported as neutropenia (1 volunteer [4.2%]) and neutrophilia (1 volunteer [4.2%]). Both adverse events were transient and considered mild by physicians.

Conclusion: The test and reference tablets met the regulatory criteria for bioequivalence as defined by the China Food and Drug Administration. Both formulations were well tolerated. Chinese Clinical Trials Registry identifier: ChiCTR-TTRCC-13003723. (*Clin Ther*. 2014;36:579–585) © 2014 Published by Elsevier HS Journals, Inc.

key words: bepotastine, bioequivalence, human plasma, LC-MS/MS, pharmacokinetics.

INTRODUCTION

Bepotastine is a second-generation histamine$_1$ (H_1) receptor antagonist that is used in the treatment of allergic rhinitis, urticaria, and pruritus associated with skin disease.[1–4] It exerts antiallergy effects through

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selective antagonism of H_1-receptors and other anti-allergic activities, including the suppression of eosinophil infiltration and interleukin 5 production.[1,5,6] Bepotastine is generally well tolerated in adult and pediatric patients with allergic conditions, without the adverse effects (AEs) of sedation and muscarinic blockade that are commonly seen with first-generation H_1-antihistamines.[7]

Bepotastine is rapidly absorbed after oral administration (T_{max} of approximately 1.2 hours).[8,9] The distribution of bepotastine to the brain is limited,[10] which may explain why no sedation AEs are found. Bepotastine undergoes minimal metabolism and is rapidly eliminated after oral administration.[9,11] It displays almost constant mean plasma elimination $t_{½}$ values ($t_{½}$ of approximately 2.5 hours) regardless of dose.[1,9,11]

A literature search of MEDLINE was conducted using the following terms: *bepotastine, bioequivalence*, *bioavailability*, *pharmacokinetics,* and *Chinese*. Although the pharmacokinetic characteristics of the drug have been studied previously,[8,9,11] no study focused on these properties in the healthy Chinese population has been reported. Therefore, the objective of the present study was to compare the bioavailability and pharmacokinetic properties of 2 tablet formulations of 10 mg of bepotastine in healthy Chinese adults. To complete the bioequivalence study, an original LC-MS/MS method was developed and validated for quantification of bepotastine in human plasma.

METHODS

Study Design

The protocol of this open-label, randomized, single-dose, 2-way crossover study was approved by the ethics committee of the First Affiliated Hospital, College of Medicine, Zhejiang University (approval No. 2013-EC-44). The study was performed in accordance with the principles of the current revision of the Declaration of Helsinki concerning medical research in humans,[12] the International Conference on Harmonization Guideline for Good Clinical Practice,[13] and the Guideline for Good Clinical Practice recommended by the China Food and Drug Administration (CFDA).[14]

The study was conducted at the Phase I Clinical Research Center of the First Affiliated Hospital from July 2013 to October 2013. Participants were admitted into the hospital at 7:00 PM the day before the study and fasted 10 hours before each drug administration. Treatments were administered with 240 mL of water. Fasting was continued for an additional 4 hours after study drug administration. Water was allowed as needed up to 2 hours before drug intake and from 2 hours after intake. A standardized lunch and dinner (mean [SD], 920 [20' kcal; 65% carbohydrate, 20% protein, and 15% fat) were provided at 4 and 10 hours after administration. The consumption of alcohol, coffee, or grapefruit-containing drinks during the trial was forbidden. Intense physical activity and smoking were not allowed during the study period. According to the randomization plan, participants were divided into 2 groups. The drug-intake sequence was determined by a randomization schedule.

Inclusion and Exclusion Criteria

Male Chinese volunteers aged 18 to 40 years with a body mass index between 19 and 25 kg/m^2 were eligible for participation. According to the Guideline for Bioavailability and Bioequivalence Studies issued by the CFDA,[15] the study included only healthy male volunteers to minimize intersubject variation. They participated regularly in pharmacokinetic studies and received a payment for their time and transportation costs regardless of whether they completed the study. The volunteers had been informed about the details, including the risks and benefits of this study, and they were free to withdraw at any time with any reason. Each volunteer was required to provide written informed consent for participation before the study. Medical history, physical examination, 12-lead electrocardiography, and various laboratory tests (hematology, blood biochemistry, hepatic function, and urinalysis) were performed before the beginning of the study. The laboratory of the First Affiliated Hospital, College of Medicine, Zhejiang University, is accredited by the National Center for Clinical Laboratories of China, which regularly tests and certifies laboratory testing facilities.

Exclusion criteria included known hypersensitivity to any ingredient in this tablet; the presence of heart, kidney, neurologic, or metabolic disease; any acute or chronic disease; and the use of other drugs within 14 days before or during the trial.

Study Drugs

According to the randomization schedule generated using SAS statistical software, version 9.1 (SAS Institute Inc, Cary, North Carolina), participants were divided